

**INTRAMOLECULAR VICARIOUS NUCLEOPHILIC SUBSTITUTION OF
HYDROGEN IN 3-NITROCHLOROACETANILIDES. A SYNTHESIS OF
OXINDOLE DERIVATIVES***

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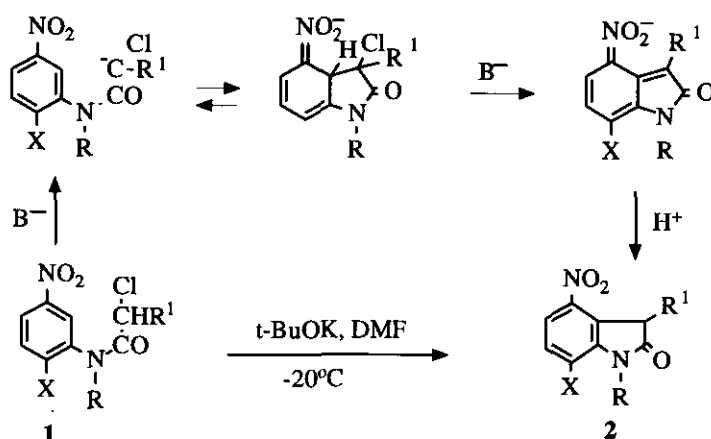
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Abstract - *3-Nitrochloroacetanilides were treated with a strong base to form the α -chlorocarbanions, which enter intramolecular reaction with the nitroaromatic rings producing nitrooxindoles.*

The vicarious nucleophilic substitution of hydrogen (VNS) is a general method for nucleophilic alkylation,¹ hydroxylation,² and amination³ of nitroarenes. We have also reported an intramolecular variant of this process for *N*-nitroaryl- and *N*-nitrobenzylchloromethanesulfonamides.⁴ In this paper we would like to report an intramolecular VNS reaction of chloroacetanilide derivatives leading to 5-membered heterocyclic systems, nitrooxindoles. Although there are no reported examples of an intermolecular VNS reaction of chloroacetamide derivatives with nitroarenes, there is a reasonable supposition that it should proceed satisfactorily in analogy to α -halonitriles and α -haloesters.⁵ Indeed, in a few preliminary experiments we have found that *N,N*-diethylchloroacetamide carbanion reacted with *p*-chloronitrobenzene replacing *ortho*-hydrogen to the nitro group to give *N,N*-diethyl-5-chloro-2-nitrophenylacetamide. Conventional nucleophilic replacement of the halogen was not observed in these experiments.

Since the VNS reaction proceeds in positions *ortho* and *para* to the nitro group, *N*-chloroacetyl- and *N*- α -chloropropionyl *m*-nitroanilines (**1a-f**) were chosen as the starting materials. They were prepared *via* acylation of *N*-propyl-3-nitro- and 2-fluoro-5-nitroanilines, and *N*-methyl-2-methoxy-5-nitroaniline with chloroacetyl and α -chloropropionyl chlorides. The corresponding substituted *N*-alkyl- nitroanilines were prepared according to known procedures: reductive *N*-propylation with propionaldehyde or *N*-methylation of the *N*-formyl derivative followed by hydrolysis. After some preliminary experiments we have found that the intramolecular VNS reactions of **1a-f** proceeded satisfactorily when carried out in the presence of an excess of *t*-BuOK in DMF. Results of these reactions are given in Scheme.

*Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday



X	R	R ¹	1	
F	Pr	H	1a	2a 63%
F	Pr	H	1b	2b 64%
MeO	Me	H	1c	2c 29%
H	Pr	Me	1d	2d 69%
F	Pr	Me	1e	2e 57%
MeO	Me	Me	1f	2f 37%

It is rather surprising that the reaction proceeded exclusively *ortho* to the nitro group even with the tertiary carbanions of **1d-f**. We were unable to find other isomers in all these experiments. Tendency for the *ortho* substitution was observed previously in the intramolecular reactions of chlorosulfonamides, however, in those cases the products of the *para* substitution were also isolated and characterized.⁴ As in other cases of the VNS reactions of halonitrobenzenes with α -chlorocarbanions we observed strong preference for the VNS of hydrogen over S_NAr of halogen even fluoride (**1b** and **1e**).

The reported reaction offers a new and simple method for synthesis of substituted oxindoles. It is in principle a process analogous to the Friedel-Crafts type cyclization of chloroacetanilide derivatives proceeding with the same stoichiometry but reverted polarity.^{6,7}

EXPERIMENTAL

Melting points are uncorrected. ¹H-Nmr spectra were recorded on Varian Gemini 200 spectrometer in CDCl₃ or C₆D₆ with TMS as a reference. Chemical shifts are given in ppm, coupling constants *J* in Hertz. High-resolution mass spectra were measured on AMD 604 spectrometer. For column chromatography silica gel 240-400 mesh (Merck) and hexane-ethyl acetate as eluent were used.

2-X-5-Nitro-N-propylanilines (X=H,F,MeO) were prepared *via* reductive propylation of the corresponding commercial anilines with propionaldehyde according to the lit.⁸ and converted to the α -chloroacetyl derivatives (**1a-f**) *via* acylation with chloroacetyl chloride and α -chloropropionyl chloride in the presence of 10% aqueous NaOH in benzene (**1a,c,d,f**) or NaH in DMF (**1b,e**).

1a: yield 64%, mp 48-49.5°C. ¹H Nmr (C₆D₆): 0.64 (t, *J*=7.4, 3H, CH₃), 1.06-1.28 (m, 2H, CH₂), 3.22-3.36 (m, 2H, CH₂), 3.30 (s, 2H, CH₂), 6.52-6.66 (m, 2H), 7.59-7.67 (m, 2H). Hrms Calcd for C₁₁H₁₃N₂O₃Cl: 256.0615. Found 256.0614.

1b: yield 66%, mp 73-75°C. ¹H Nmr (C₆D₆): 0.63 (t, *J*=6.8, 3H, CH₃), 1.04-1.26 (m, 2H, CH₂), 3.35 (s, 2H,

CH₂), 6.25 (apparent t, *J*=8.8, 1H), 7.42-7.52 (m, 1H), 7.68 (d, *J*=2.9, 1H). Hrms Calcd for C₁₁H₁₂N₂O₃ClF: 274.0520. Found 274.0520

1c: yield 77%, semisolid. ¹H Nmr (C₆D₆): 3.30 (s, 2H, CH₂), 3.35 (s, 3H, NCH₃), 3.97 (s, 3H, OCH₃), 6.96 (d, *J*=9.2, 1H, H-5**), 7.70-8.14 (m, 2H, H-2,6). Hrms Calcd for C₁₀H₁₁N₂O₄Cl: 258.0375. Found 258.0392

1d: yield 72%, oil ¹H Nmr (C₆D₆ mixture of rotamers 70/30); main rotamer: 0.94 (t, *J*=7.1, 3H, CH₃), 1.12-1.32 (m, 2H, CH₂), 1.49 (d, *J*=7.1, 3H, CH₃), 3.14-3.36 (m, 2H, CH₂), 3.90 (q, *J*=7.1, 1H, CH), 6.74 (apparent t, *J*=8.2, 1H, H-5), 7.58 (ddd, *J*=8.2, 2.2, 0.9, 1H, H-6), 7.72 (dd, *J*=8.2, 2.2, 1H, H-4), 8.11 (apparent t, *J*=2.2, 1H, H-2), and minor rotamer: 0.67 (t, *J*=7.3, 3H, CH₃), 0.82-0.94 (m, 2H, CH₂), 1.44 (d, *J*=6.7, 3H, CH₃), 3.70-3.95 (m, 2H, CH₂), 4.11 (q, *J*=6.9, 1H, CH), 6.71 (apparent t, *J*=8.2, 1H, H-5), 6.94 (d, *J*=8.2, 1H, H-4), 7.38 (ddd, *J*=8.2, 2.2, 0.9, 1H, H-6), 7.86 (apparent t, *J*=2.2, 1H, H-2). Hrms Calcd for C₁₂H₁₅N₂O₃Cl: 270.0715. Found 270.0715.

1e: yield 77%, oil. ¹H Nmr (C₆D₆ shows existence of rotamers): 2H, 0.66 (t, *J*=7.2, 3H, CH₃), 1.12-1.36 (m, 2H, CH₂), 1.44 and 1.48 (2 x d of rotamers, *J*=6.9, 3H, CH₃), 3.07-3.97 (m, CH₂), 3.47 (q, *J*=6.9, 1H, CH), 6.29-6.48 (m, 1H), 7.51-7.63 (m, 1H), 7.75 and 8.15 (2 x dd of rotamers, *J*=4.2, 1.6, 1H). Hrms Calcd for C₁₂H₁₄N₂O₃ClF: 288.0677. Found 288.0674.

1f: yield 54%, mp 149-151°C. ¹H Nmr (C₆D₆ mixture of rotamers): 1.41 and 1.46 (2 x d of rotamers, *J*=6.4, 3H, CH₃), 2.79 and 2.83 (2 x s of rotamers, 3H, NCH₃), 2.93 and 2.97 (2 x s of rotamers, 3H, OCH₃), 3.81 and 3.94 (2 x q of rotamers, *J*=6.4, 1H, CH), 5.83 and 5.92 (2 x d of rotamers *J*=9.2, 1H, H-5), 7.78 (d, *J*=9.2, 1H, H-6), 8.13 (d, *J*=1.8, 1H, H-2). Hrms Calcd for C₁₁H₁₃N₂O₄Cl: 272.0564. Found 272.0564.

***N,N*-Diethyl-(5-chloro-2-nitrophenyl)acetamide.** A solution of *p*-chloronitrobenzene (3.2 g 20 mmol) and *N,N*-diethylchloroacetamide (3.0 g 20 mmol) in dry DMF (20 ml) was added at -20°C to a stirred solution of *t*-BuOK (11.2 g, 100 mmol), in dry DMF (30 ml). After 25 min the addition was completed and blue mixture was stirred for an additional hour at -20°C, and poured into cold hydrochloric acid (200 ml). After extraction with AcOEt (3 x 30 ml) and evaporation of the solvent the residue was chromatographed (AcOEt-hexane 1:8) to give the product 4.6 g, yield 85% oil, ¹H Nmr (CDCl₃): 1.11 (t, *J*=7.1, 3H, CH₃), 1.29 (t, *J*=7.1, 3H, CH₃), 3.31-3.48 (m, 4H, 2 x CH₂), 4.03 (s, 2H, CH₂), 7.31 (d, *J*=2.3, 1H), 7.38 (dd, *J*=3.7, 2.3, 1H), 8.03 (d, *J*=8.7, 1H). Hrms (m/z): 270.0771 (M⁺, C₁₂H₁₅N₂O₃Cl, calcd 270.0772). Anal. Calcd for C₁₂H₁₅N₂O₃Cl: C, 53.24; H, 5.58; N, 10.35. Found: C, 52.99; H, 5.70; N, 10.35.

1-Alkyl-4-Nitro-7-X-oxindoles. General procedure for intramolecular VNS reaction.

To a stirred solution of *t*-BuOK (5.6 g, 50 mmol) in dry DMF (20 ml) a solution of **1a-f** (10 mmol) in dry DMF (10 ml) were added at -20°C during 15-20 min. After the addition was completed the deep violet or blue mixtures were stirred for additional hour at -20°C, and next treated as describe above. The received products were purified by column chromatography (AcOEt-hexane=1:4) followed by recrystallization from 96% EtOH to yield **2a-f**.

2a: yield 62%, mp 112-113°C (96% EtOH). ¹H Nmr (CDCl₃): 0.99 (t, *J*=7.4, 3H, CH₃), 1.72 (sext, *J*=7.4, 2H, CH₂), 3.73 (t, *J*=7.4, 2H, CH₂), 4.01 (s, 2H, CH₂), 7.12 (d, *J*=7.9, 1H), 7.47 (dd, *J*=8.4, 7.9, 1H), 7.85 (d, *J*=7.9, 1H). Hrms (m/z): 220.0851 (M⁺, C₁₁H₁₂N₂O₃, Calcd 220.0847). Anal. Calcd for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.50; N, 12.72. Found: C, 59.85; H, 5.49; N, 12.42.

2b: yield 64%, mp 116-117°C (96% EtOH). ¹H Nmr (CDCl₃): 0.89 (t, *J*=7.5, 3H, CH₃), 1.62 - 1.82 (m, 2H, CH₂), 3.86 (dt, *J*=7.5, 1.6, 2H, CH₂), 4.05 (s, 2H, CH₂), 7.19 (d apparent t, *J*=9.3, 7.2, 1H), 7.84 (dd, *J*=9.3, 3.9, 1H). Hrms (m/z): (238.2175 (M⁺, C₁₁H₁₁N₂O₃F, calcd 238.2179). Anal. Calcd for C₁₁H₁₁N₂O₃F: C, 55.46; H, 4.65; N, 11.76. Found: C, 55.30; H, 4.68; N, 11.50.

2c: yield 30%, mp 176-178°C (96% EtOH). ¹H Nmr (CDCl₃): 3.51 (s, 3H, NCH₃), 3.97 (s, 5H, CH₂, OCH₃), 6.96 (d, *J*=9.2, 1H), 7.93 (d, *J*=9.2, 1H). Hrms (m/z): 222.1975 (M⁺, C₁₀H₁₀N₂O₄, calcd 222.1990). Anal. Calcd

**NO₂ - position 1 for all assignment of H in the aromatic rings.

for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 53.97; H, 4.41; N, 12.62.

2d: yield 68%, mp 72-72.5°C (96% EtOH). 1H Nmr ($CDCl_3$): 0.97 (t, $J=7.4$, 3H, CH_3), 1.52 (d, $J=7.4$, 3H, CH_3), 1.72 (sex, $J=7.4$, 2H, CH_2), 3.61 and 3.84 (m, 2H, CH_2), 4.03 (q, $J=7.4$, 1H, CH), 7.13 (d, $J=7.8$, 1H, H-4^{*}), 7.45 (apparent t, $J=7.8$, 1H, H-5), 7.81 (dd, $J=8.4$, 0.9, 1H, H-6). Hrms (m/z): 234.1002 (M^+ , $C_{12}H_{14}N_2O_3$, calcd 234.1004). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.52; H, 6.00; N, 11.74.

2e: yield 57%, mp 96-97°C (96% EtOH). 1H Nmr ($CDCl_3$): 0.96 (t, $J=7.5$, 3H, CH_3), 1.53 (d, $J=7.4$, 3H, CH_3), 1.62-1.90 (m, 2H, CH_2), 3.81-3.91 (m, 2H, CH_2), 4.07 (dq, $J=7.4$, 0.6, 1H, CH), 7.20 (ddd, $J=10.5$, 9.2, 0.6, 1H, H-5), 7.83 (dd, $J=9.2$, 3.9, 1H, H-6). Hrms (m/z): 252.0908 (M^+ , $C_{12}H_{13}N_2O_3F$ calcd 252.0910). Anal. Calcd for $C_{12}H_{13}N_2O_3F$: C, 57.17; H, 5.20; N, 11.11. Found: C, 57.07; H, 5.24; N, 11.22.

2f: yield 37%, mp 166-167°C (96% EtOH). 1H Nmr ($CDCl_3$): 1.50 (d, $J=7.4$, 3H, CH_3), 3.51 (s, 3H, NCH_3), 3.97 (s, 3H, OCH_3), 4.02 (q, $J=7.4$, 1H, CH), 6.93 (d, $J=9.2$, 1H, H-5), 7.83 (d, $J=9.2$, 1H, H-6). Hrms (m/z): 236.0790 (M^+ , $C_{11}H_{12}N_2O_4$, calcd 236.0797). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.96; H, 5.12; N, 11.87. Found: C, 55.69; H, 5.04; N, 11.63.

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